POLICY AND PROCEDURES

Office of Pharmaceutical Quality

Office of Biotechnology Products and Office of Compliance, Office of Manufacturing Quality Interactions on BLA Assessments

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PURPOSE

This MAPP outlines policies and procedures in the Office of Biotechnology Products (OBP) in the Office of Pharmaceutical Quality (OPQ) and the Office of Manufacturing Quality (OMQ) in the Office of Compliance (OC) designed to:

- Ensure product quality as it relates to safety and efficacy of the product.
- Provide a team approach to product quality evaluation of biologics licensing applications.
- Define clear roles and responsibilities.
- Establish work processes that are effective.
- Develop a system that ensures problems are resolved in a timely and professional manner.

BACKGROUND

The Office of Biotechnology Products in OPQ and the Office of Manufacturing Quality in OC collaborate in the evaluation of biologics license applications (BLAs). OBP and OMQ have implemented a process improvement initiative to better coordinate evaluation of applications. This initiative includes development of the following:

- A timely and responsive system to ensure product quality throughout the product life cycle.
- A process that allows for efficiency, consistency, and innovation within the Agency and in industry.
- The use of science-based risk management and quality principles.
- Synergistic (multi-disciplined) collaboration.
- A shift from review-based approvals for "low risk" postmarketing changes to annual report evaluations and compliance- and inspection-based confirmations and/or evaluations.

POLICY

- The Office of Biotechnology Products in the Office of Pharmaceutical Quality, and the Office of Manufacturing Quality in the Office of Compliance will work together to evaluate both original BLAs and supplements.

RESPONSIBILITIES

- **The responsibilities of the Office of Compliance OMQ include the following:**
    - Review facility, equipment, and procedures in coordination with BLA and supplement submissions.
    - Lead in the assessment of the manufacturing and control of **drug product** as it relates to contamination/cross contamination control, sterility assurance, and microbiological product quality, and conversion and use of facilities for multiproduct production.[1] **Drug substance** assessment is largely led by OBP, but with OMQ involvement. Both include desk review plus inspection.
    - Provide IND assistance, as requested by OBP.
    - Plan collaborative inspections based on firm's compliance history and chemistry, manufacturing, and controls (CMC) facility information.
    - Share evaluation of CMC process validation and robustness with OBP (see Attachment A).
    - Provide the lead on inspection policy, and enforcement of current good manufacturing practice (cGMP) policy.

[1] Follow Tables 1 and 2 (Attachment B) for signoff responsibility.

- Take the lead on evaluation and enforcement of the Pharmaceutical Quality System.

- **The responsibilities of the Office of Biotechnology Products (OBP) will include the following:**

  - Review product structure, relationship between structure and function, and impurities (including contaminants).

  - Review process controls throughout the biological product life cycle for impact on structure/function and impurities.

  - Participate in inspections over the biological product life cycle (preapproval inspection (PAI) and surveillance) with a focus on issues related to structure and function. This may include the following:

    - Assistance in evaluation of deviations, investigations, and process robustness/control.
    - Batch record/life cycle relationship to attributes.
    - Analytical assays.

  - Take part in inspections for reviewer education.

  - Participate in Biological Product Deviation Report (BPDR) evaluations (led by OC, with assistance from OBP on assessment of product impact).

PROCEDURES

- The following are required communications between OBP and OMQ:

  - Early supplement category risk assessment for applications.
  - Early identification of assigned team members.
  - Pre-inspection discussion specifying inspection focus (if appropriate).
  - PAI assignment information.
  - Notification of important or cross-cutting issues/discussions.
  - Exchange of final review and recommendations.
  - Sharing of draft and finalized letters to ensure continuity.

- The following meetings include OBP and OMQ:

  - Pre-phase 3 meeting
  - Pre-BLA meeting
  - BLA filing, mid-cycle and other CMC review cycle meetings
  - Facilities-specific meetings
  - Administrative meetings at planned intervals
  - Go-away meetings, as needed

- The following are procedures for Form FDA 483 items on inspection:
    - The lead inspection office is the Office of Compliance (OC) or FDA Office of Regulatory Affairs (ORA).
    - The lead inspector makes final decision on 483 items.
    - Non-483 inspectional issues can be included in the establishment inspection report (EIR) as "For Further CDER Consideration" comments.
    - If OBP participates in developing a 483 observation, OBP should provide comments on the company's response through CDER/OC and/or FDA ORA (depending on who led the inspection).
- The following are procedures for shared BLA supplement[2] letters. Shared supplements include topics with OBP as the lead office and topics with OC/OMQ as the lead office (see Attachment B):
    - When OBP is lead on a supplement, OBP signs off on the letter with OC/OMQ concurrence.
    - When the OC/OMQ is the lead on a supplement, OC/OMQ signs off on the letter with OBP concurrence.
    - OBP has lead on all shared supplements unless a different arrangement is agreed to.
    - Each component retains responsibility for comments (on the letter) in their lead areas.
    - The letter must be circulated to all OMQ/OBP reviewers and responsible managers.
- The following are interest reconciliation procedures to resolve conflicts prior to formal dispute resolution:
    - OMQ and OBP Team Leaders and above will be trained in the process of "Interest Reconciliation." "Interest Reconciliation" specifies general steps to resolve conflict so agreements can be reached without formal dispute resolution.
    - Interest reconciliation includes the following:
        - Team members involved in the conflict work with each other to find a resolution to ensure that their interests in the resolution of the conflict are satisfied.
        - If an agreement is not reached, the issue will be referred to their primary Team Leaders.

[2] Original BLA submissions are signed off by Office of New Drugs (OND).

- The Team Leaders review the facts related to the conflict to determine whether they can resolve the issue at their level.

- If they cannot resolve the conflict the issue will be referred to the appropriate next level being sure to keep any intermediate levels of leadership aware of the referral and the process.

- When the conflict is resolved, an explanation of "how and why" the final decision was made is communicated to all involved in the process.

REFERENCES

1. Form FDA 483, Inspectional Observations
2. Guidance for industry on *Formal Dispute Resolution: Scientific and Technical Issues Related to Pharmaceutical CGMP*
3. ICH Q10 Pharmaceutical Quality System

DEFINITIONS

- BLA – Biologics License Application
- BPDR – Biological Product Deviation Reporting
- CMC – Chemistry, Manufacturing, and Controls
- cGMP – Current Good Manufacturing Practice
- IND – Investigational New Drug
- OBP – Office of Biotechnology Products
- OC – Office of Compliance
- OMQ – Office of Manufacturing Quality
- OPQ– Office of Pharmaceutical Quality
- ORA – Office of Regulatory Affairs
- PAI – Pre-approval Inspection
- TB-EER – Therapeutic Biologic Establishment Evaluation Request
- Compendial - United States Pharmacopeia (USP)

SUMMARY OF CHANGES

1. Changed Office of Pharmaceutical Science to Office of Pharmaceutical Quality
2. Changed Office of Compliance/Division of Manufacturing Product Quality to Office of Compliance/Office of Manufacturing Quality

EFFECTIVE DATE

This MAPP is effective upon date of publication.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
10/22/15	1	Updated format into the current template and transferred MAPP ownership to OPQ.

ATTACHMENT A

Roles and Responsibilities for Assessment of BLA Process Validation and Facility/Equipment Qualification

The assessments are grouped under the lead for review. When an advisor is involved, they assist the lead. In an integrated approach, all processes are subject to inspection.
For inspections, OC or ORA is lead and OBP participates as specified on page 3 under OBP responsibilities.

OMQ Assessment Lead:

- Microbial method qualification (CFR, or compendial methods for sterility, endotoxin, bioburden); equivalent methods for microbial qualification are shared with OBP (see Attachment B).
- Container-Closure Integrity, preservative effectiveness, shipment, and materials handling; OBP is lead on shipping stability.
- Finishing process design as it relates to drug product sterility (e.g., sterility assurance evaluation).
- Facility and equipment qualification and validation: contamination/cross contamination control.
- Drug Substance/Drug Product hold conditions at scale for contamination control; OBP is advisor.
- Validation for Cleaning/Sanitization of column chromatography and membrane systems during lifetime use.
- Product simulations for filling/finishing process and for fermentation/buffer tanks.
- Chosen equipment to produce process/parameters.
- Validation of sterilization processes used in drug product manufacturing.
- Validation of disposables for use in manufacturing; OPB is lead for leachables and extractables.
- Supplier (site) qualifications; OBP is lead for intermediates and synthesis process.

OBP Assessment Lead:

- Overall process design and flow for drug substance, non-sterility parameters of drug product: e.g., finishing process design as it relates to stability, extractables, leachables, and interaction with product; OMQ is advisor.
- In-process controls for relevant operating and performance parameters; OMQ is advisor.
- Hold time validation for product attributes; OMQ is advisor for microbial control.
- Impurity and viral clearance validation.
- Lifetime use of chromatograph resins including impurity carryover. Shared with OMQ.[3]
- Product quality assessment through in-process material characteristics as expressed in process parameters (targets).
- Validation of consistency of submitted batches for commercial process; OMQ is advisor.
- Method validation excluding compendial or CFR sterility, bioburden, and endotoxin method qualifications.
- Qualification of intermediates.
- Raw materials fitness for use.

[3] This is related to above OMQ Assessment bullet regarding "Assessment of Validation for Cleaning/Sanitization of column chromatography and membrane systems during lifetime use."

ATTACHMENT B

Additional Clarification in CTD Format

Manufacturing and Product Quality Assessment Responsibilities Between OBP and BMT: BLA or Submission Content From CDT Format Module 3: Format of Quality Section; 3.2 Body of Data

Table 1: Drug Substance Quality Assessments

3.2.S. Drug Substance		OBP	OMQ
S.1 General Information	1. Nomenclature	X[4]	Background information for microbial[5] control – no assessment
	2. Structure	X	
	3. General Properties	X	
S.2 Manufacture	1. Manufacturers	Provide support for inspection planning and participation	X Conduct TB-EER; Identify sites for PAI inspection; plan inspection and identify and lead team
	2. Description of Manufacturing Process and Process Controls	X	Background for inspection and assess microbial control strategy
	3. Control of Materials	X Including microbial, prion and viral evaluation of cell bank and other biological materials as per 3.2.A.2	Background for inspection and assess microbial control strategy
	4. Controls of Critical Steps and Intermediates	X	Background for inspection and assess microbial control strategy
	5. Process Validation and /or Evaluation	X	Background for inspection and assess validation at scale of the microbial control strategy
	6. Manufacturing Process Development	X	Background for inspection
S.3 Characterization	1. Elucidation of Structure and other Characteristics	X	

[4] X denotes the lead office except where otherwise noted in the columns.
[5] In this MAPP, microbial refers to bacteria and fungi, not viruses or prions.

3.2.S. Drug Substance		OBP	OMQ
	2. Impurities	X	
S.4 Control of Drug Substance	1. Specification	X Equivalent microbial specifications are shared[6]	CFR, compendial, or equivalent microbial specifications only
	2. Analytical Procedures	X Equivalent microbial methods are shared[6]	CFR, compendial, or equivalent microbial analytical procedures only
	3. Validation of Analytical Procedures	X Equivalent microbial methods are shared[6]	Validation of CFR, compendial, or equivalent microbial analytical procedures only
	4. Batch Analyses	X	Microbial Attributes only
	5. Justification of Specification	X Equivalent microbial specifications are shared[6]	CFR, compendial, or equivalent microbial specifications only
S.5 Reference Standards or Materials		X	
S.6 Container Closure System		X	
3.2.S.7 Stability	1. Stability Summary and Conclusions	X	Microbial attributes only
	2. Post-approval Stability Protocol and Stability Commitment	X	Microbial attributes only
	3. Stability Data	X	

[6] For equivalent microbial methods, review will be shared. In general, for extracellular organisms OMQ will lead and for intracellular organisms or for equivalent endotoxin methods OBP will lead.

Table 2: Drug Product Quality Assessments

3.2.P DRUG PRODUCT		OBP	OMQ
P.1 Description and Composition of the Drug Product		X	Background information for sterility assurance review
P.2 Pharmaceutical Development	1. Components of the Drug Product	X	
	2. Drug Product	X	X
	3. Manufacturing Process Development	X	Background for inspection
	4. Container Closure System	X	X
	5. Microbiological Attributes		X Container Closure integrity: microbial ingress/dye ingress, etc. Preservative effectiveness
	6. Compatibility	X	
P.3 Manufacture	1. Manufacturers	Provide support for inspection planning and participation	X Conduct TB-EER; Identify sites for PAI inspection; plan inspection and identify and lead team
	2. Batch Formula	X	
	3. Description of Manufacturing Process and Process Controls	X	Background information for inspection and for sterility assurance review
	4. Controls of Critical Steps and Intermediates	X	Background information for sterility assurance review
	5. Process Validation and/or Evaluation	X	Review sterilization process/aseptic process validation data for sterility assurance
P.4 Control of Excipients	1. Specifications	X	
	2. Analytical Procedures	X	
	3. Validation of Analytical Procedures	X	
	4. Justification of Specifications	X	
	5. Excipients of Human or Animal Origin	X	

3.2.P DRUG PRODUCT		OBP	OMQ
	6. Novel Excipients	X	
P. 5 Control of Drug Product	1. Specifications	X Equivalent microbial specifications are shared[6]	CFR, compendial, or equivalent microbial specifications only
	2. Analytical Procedures	X Equivalent microbial methods are shared[6]	CFR, compendial, or equivalent microbial analytical procedures only
	3. Validation of Analytical Procedures	X Equivalent microbial methods are shared[6]	Validation of CFR, compendial, or equivalent microbial Analytical Procedures
	4. Batch Analyses	X	CFR, compendial, or equivalent microbial specifications only
	5. Characterization of Impurities	X	
	6. Justification of Specifications	X Equivalent microbial specifications are shared[6]	CFR, compendial, or equivalent microbial specifications only
P.7 Container Closure System		X	
P.8 Stability	1. Stability Summary and Conclusion	X	Microbial attributes only
	2. Post-approval Stability Protocol and Stability Commitment	X	Microbial attributes only
	3. Stability Data	X	Microbial attributes only
A APPENDICES	1. Facilities and Equipment		X Contamination /cross contamination; multiproduct facilities
	2. Adventitious Agents Safety Evaluation	X	
	3. Novel Excipients	X	
R REGIONAL INFORMATION		X	
3.3 LITERATURE REFERENCES		X	When necessary